PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 20 June 2001 (20.06.01)	
International application No. PCT/EP00/08190	**Applicant's or agent's file reference** SPW99.05
International filing date (day/month/year) 22 August 2000 (22.08.00)	**Priority date** (day/month/year) 23 August 1999 (23.08.99)
Applicant VAN HES, Roelof et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

13 March 2001 (13.03.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Juan Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

12

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SPW99.05		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/08190	22/08/2000	23/08/1999
International Patent Classification (IPC) or national classification and IPC C07D405/12		
Applicant SOLVAY PHARMACEUTICALS B.V.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

I	☒	Basis of the report
II	☐	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
VI	☐	Certain documents cited
VII	☒	Certain defects in the international application
VIII	☒	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13/03/2001	07.01.2002
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Bosma, P Telephone No. +31 70 340 3665

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/08190

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-20 as originally filed

Claims, No.:

1-7 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-7
	No:	Claims	
Inventive step (IS)	Yes:	Claims	2-4
	No:	Claims	1, 5-7
Industrial applicability (IA)	Yes:	Claims	1-7
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive st p or industrial applicability; citations and explanations supporting such statem nt

Reference is made to the following documents:
D1.....DE-A-19730989
D2.....EP-A-376607
D3.....DE-A-4333254
D4.....WO-A-99/05140

Novelty

The subject matter of the present claims 1-7 has not been described in the available prior art documents, therefore the present application satisfies the criterion set forth in Article 33(2) PCT and is considered to be new in respect of the prior art as defined in the regulations (Rule 64(1)-(3) PCT).

Inventive step

a) Document D1, which is considered to represent the most relevant state of the art, discloses (cf. page 1; claims; examples 2-5) phenylpiperazine derivatives, useful as inhibitors of serotonin reuptake, of the present formula I, wherein X represents a group of the present formula (5), which is attached to the piperazine group via the **6-position** of the benzopyranone moiety.
In the compounds of the present claim 1, this moiety is attached to the piperazine group via the **5-position**, and this only leads to a trivial structure modification of the compounds of the state of the art.
Therefore the present compounds are considered to be a further development of the teaching of D1, at which the man skilled in the art would arrive, without the exercise of inventive skill.
Thus, the subject-matter of claims 1, 5-7 does not involve an inventive step and does not satisfy the criterion set forth in Article 33(3) PCT.

b) D2 discloses the use of 1,4-benzodioxan-5-yl-1-piperazinyl derivatives as serotonin reuptake inhibitors, which compounds differ from the ones in the present application, in which X is a group of the formula (2), by the absence of the substituent CH_2OR.

D3 discloses structurally very closely related compounds as serotonin reuptake inhibitors, in which the corresponding group attached to the piperazine group can be substituted by such a group CH_2OR.
It appears to be obvious to the person skilled in the art, namely when the same result is to be achieved, to apply these features with corresponding effect to the compounds according to document D2 and thus to arrive at the compounds according to the present claims 1, 5-7, in which X is a group of the formula (2). The subject-matter of these claims therefore does not appear to involve an inventive step (Article 33(3) PCT).

Therefore it seems necessary for the assessment of inventive step for the above indicated subject-matter to have evidence for the presence of unexpected effects or properties in relation to those described in the state of the art, or to delete the above indicated subject-matter from the scope of the claimed invention.

Industrial applicability
The compounds of the present application are useful as serotonin reuptake inhibitors and are having affinity for the dopamine D2-receptor.
For the assessment of the present claim 7 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII
Certain defects in the international application

a) Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D4 has not been mentioned in the description, nor have these documents been identified therein.

b) In claim 3 the wording "...having formula (I)" should have been changed into "...having formula (1)".

R Item VIII

Certain observations on the international application

a) The terms "Y is C, ..." in partial formula 1), and "Z is C, ..." in partial formula 3), and "Q=C" or "T=C" or "T and Q are carbon" in partial formula 7) as used in claim 1 are vague and unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, because hydrogens are indicated, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
SPW99.05		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/08190	22/08/2000	23/08/1999
Applicant		
SOLVAY PHARMACEUTICALS B.V.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   PHENYLPIPERAZINES AS SEROTONIN REUPTAKE INHIBITORS

5. With regard to the **abstract,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. –

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

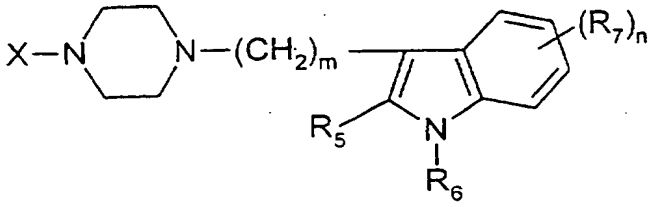
INTERNATION EARCH REPORT

International application No.
CT/EP 00/08190

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

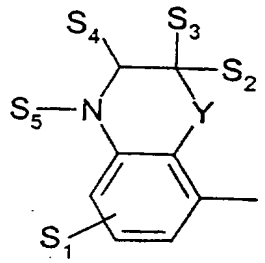
The invention relates to a group of phenylpiperazines having high affinity for the dopamine D2-receptor and are good serotonin reuptake inhibitors (SRI's).
The invention relates to a group of phenylpiperazine derivatives of the formula

(I)



(I)

wherein: a.o.
-x is 1) a group of the formula



(1)

wherein

- S_1 is hydrogen or halogen,
- S_2 and S_3 are independently hydrogen, alkyl (1-6C), phenyl or benzyl,
- S_4 represents two hydrogen atoms or an oxo group,
- S_5 is H or alkyl (1-4C), and

- Y is C, O or S, and salts there of.

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]T/EP 00/08190

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D405/12 C07D401/12 C07D413/12 C07D417/12 C07D209/34
C07D403/12 C07D209/40 A61K31/496

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 99 67237 A (KROG JENSEN CHRISTIAN ;MIKKELSEN IVAN (DK); LUNDBECK & CO AS H (DK) 29 December 1999 (1999-12-29) claims 1,12,14-18; examples 1-5 ---	1,5-7
X	WO 99 05140 A (MIKKELSEN IVAN ;LUNDBECK & CO AS H (DK); MOLTZEN EJNER KNUD (DK);) 4 February 1999 (1999-02-04) claims 1,14-19; examples 1-7 ---	1,5-7
X	DE 197 30 989 A (MERCK PATENT GMBH) 21 January 1999 (1999-01-21) page 1; claims; examples 2-5 ---	1,5-7
Y	EP 0 376 607 A (LUNDBECK & CO AS H) 4 July 1990 (1990-07-04) the whole document; claims; examples 2-5 --- -/--	1,5-7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 January 2001	23/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bosma, P

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]T/EP 00/08190

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	DE 43 33 254 A (MERCK PATENT GMBH) 6 April 1995 (1995-04-06) the whole document; claims; examples 2-5	1,5-7
A	DE 41 27 849 A (MERCK PATENT GMBH) 25 February 1993 (1993-02-25) the whole document; claims; examples 2-5	1,5-7

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/08190

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9967237 A	29-12-1999	AU 4359299 A	10-01-2000
WO 9905140 A	04-02-1999	AU 8534098 A	16-02-1999
		BR 9810790 A	25-07-2000
		CN 1265107 T	30-08-2000
		EP 1007523 A	14-06-2000
		NO 20000372 A	21-03-2000
		PL 338194 A	09-10-2000
		ZA 9806237 A	31-03-1999
DE 19730989 A	21-01-1999	AU 8730298 A	10-02-1999
		BR 9810607 A	11-07-2000
		CN 1264379 T	23-08-2000
		WO 9903855 A	28-01-1999
		EP 0998474 A	10-05-2000
		NO 20000216 A	17-01-2000
		PL 338075 A	25-09-2000
		SK 352000 A	12-06-2000
		ZA 9806390 A	24-05-1999
EP 0376607 A	04-07-1990	AT 102184 T	15-03-1994
		AU 637991 B	17-06-1993
		AU 4719889 A	05-07-1990
		CA 2006356 A	28-06-1990
		DE 68913487 D	07-04-1994
		DE 68913487 T	04-08-1994
		DK 645689 A	29-06-1990
		ES 2062050 T	16-12-1994
		FI 93005 B	31-10-1994
		IE 62668 B	22-02-1995
		IL 92990 A	24-01-1995
		JP 2225460 A	07-09-1990
		JP 2895121 B	24-05-1999
		NO 174772 B	28-03-1994
		NZ 231855 A	25-02-1992
		PT 92728 A,B	29-06-1990
		US 5002948 A	26-03-1991
		ZA 8909960 A	28-11-1990
DE 4333254 A	06-04-1995	AT 153663 T	15-06-1997
		AU 679774 B	10-07-1997
		AU 7424494 A	13-04-1995
		BR 1100891 A	06-06-2000
		CA 2133152 A	31-03-1995
		CN 1106811 A,B	16-08-1995
		CZ 9402370 A	12-04-1995
		DE 59402902 D	03-07-1997
		DK 648767 T	22-12-1997
		EP 0648767 A	19-04-1995
		ES 2105454 T	16-10-1997
		GR 3024551 T	31-12-1997
		HU 71833 A	28-02-1996
		JP 7149762 A	13-06-1995
		NO 943616 A	31-03-1995
		PL 305216 A	03-04-1995
		RU 2132848 C	10-07-1999
		SK 118494 A	10-05-1995
		US 5532241 A	02-07-1996

INTERNATIONAL SEARCH REPORT

[redacted]nation on patent family members

International Application No
[redacted]T/EP 00/08190

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 4333254 A		ZA 9407622 A	16-05-1995
DE 4127849 A	25-02-1993	AU 653847 B	13-10-1994
		AU 2121092 A	25-02-1993
		CA 2076573 A	23-02-1993
		CZ 9202578 A	17-03-1993
		EP 0529462 A	03-03-1993
		HU 64334 A	28-12-1993
		JP 5230059 A	07-09-1993
		MX 9204844 A	01-04-1993
		NO 923283 A	23-02-1993
		PL 295673 A	17-05-1993
		RU 2056420 C	20-03-1996
		US 5242925 A	07-09-1993
		ZA 9206334 A	22-04-1993

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 March 2001 (01.03.2001)

PCT

(10) International Publication Number
WO 01/14330 A2

(51) International Patent Classification[7]: C07D 209/00

(21) International Application Number: PCT/EP00/08190

(22) International Filing Date: 22 August 2000 (22.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

99202710.2	23 August 1999 (23.08.1999)	EP
1012888	23 August 1999 (23.08.1999)	NL

(71) Applicant *(for all designated States except US)*: SOLVAY PHARMACEUTICALS B.V. [NL/NL]; C.J. Van Houtenlaan 36, NL-1381 CP Weesp (NL).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: VAN HES, Roelof [NL/NL]; P.O. Box 140, NL-1380 AC Weesp (NL). VAN DER HEIJDEN, Johannes, A., M. [NL/NL]; P.O. Box 140, NL-1380 AC Weesp (NL). KRUSE, Cornelis, G. [NL/NL]; P.O. Box 140, NL-1380 AC Weesp (NL). TIPKER, Jacobus [NL/NL]; P.O. Box 140, NL-1380 AC Weesp (NL). TULP, Martinus, T., M. [NL/NL]; P.O. Box 140, NL-1380 AC Weeso (NL). VISSER, Gerben, M. [NL/NL]; P.O. Box 140, NL-1380 AC Weesp (NL). VAN VLIET, Bernard, J. [NL/NL]; P.O. Box 140, NL-1380 AC Weesp (NL).

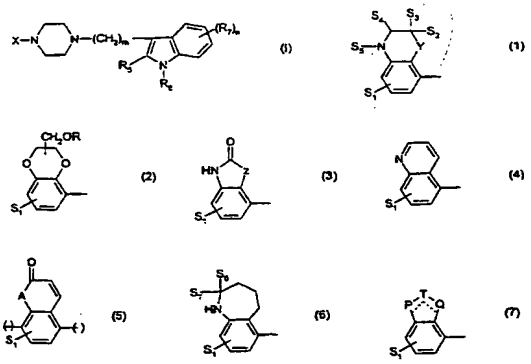
(74) Agent: MUIS, Maarten; Octrooibureau Zoan B.V., P.O. Box 140, NL-1380 AC Weesp (NL).

(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: NEW PHENYLPIPERAZINES



(57) Abstract: The invention relates to a novel group of phenylpiperazines having interesting pharmacological properties. The invention relates to a group of novel phenylpiperazine derivatives of formula (I): wherein: X is 1) a group of formula (1) wherein: S_1 is hydrogen or halogen, S_2 and S_3 are independently hydrogen, alkyl (1-6C), phenyl or benzyl, S_4 represents two hydrogen atoms or an oxo group, S_5 is H or alkyl (1-4C), and Y is C, O or S, or 2) a group of formula (2) wherein S_1 has the above meaning and R is H, alkyl (1-4C), alkoxyalkyl (2-6C), alkenyl (2-4C) or alkynyl (2-4C), or 3) a group of formula (3) wherein S_1 has the above meaning and Z is C, O or N, or 4) a group of formula (4) wherein S_1 has the above meaning, or 5) a group of formula (5) wherein S_1 has the above meaning and A is O or N, linked to the piperazine ring with position 5 or 8, or 6) a group of formula (6) wherein S_1 has the above meaning and S_6 and S_7 represent hydrogen atoms or an oxo group, or 7) a group of formula (7) wherein one of the dotted lines can represent a double bond, S_1 has the above meaning, and P=T=Q=nitrogen or P=T=nitrogen and Q=C or P=Q=nitrogen and T=C or C-CH_3 or P=nitrogen, and T and Q are carbon or P=nitrogen, T is carbon and Q is sulphur, m has the value 2 to 6; n has the value 0-2; R_5 and R_6 are independently H or alkyl (1-3C); or R_5+R_6 represent a group -(CH_2)-$_p$ wherein p has the value 3-5, and R_7 is alkyl (1-3C), alkoxy (1-3C), halogen or cyano; or R_6+R_7 (R_7 at position 7 of the indole group) represent a group -$(CH_2)_q$, wherein q has the value 2-4, and salts thereof.

WO 01/14330 A2

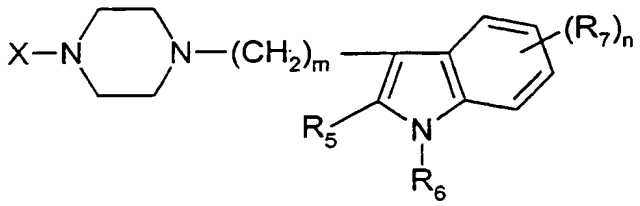
Published:

— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

New phenylpiperazines

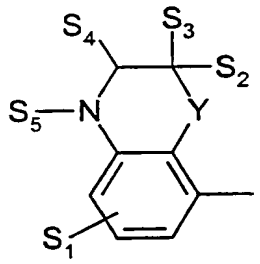
The invention relates to a group of novel phenylpiperazine derivatives of the formula (I):



(I)

wherein:

- X is 1) a group of the formula

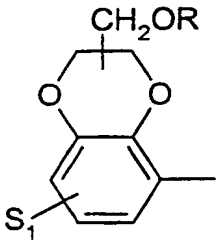


(1)

wherein

- S_1 is hydrogen or halogen,
- S_2 and S_3 are independently hydrogen, alkyl (1-6C), phenyl or benzyl,
- S_4 represents two hydrogen atoms or an oxo group,
- S_5 is H or alkyl (1-4C), and
- Y is C, O or S,

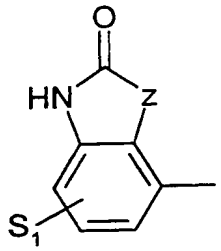
or 2) a group of the formula



(2)

wherein S_1 has the above meaning and R is H, alkyl (1-4C), alkoxyalkyl (2-6C), alkenyl (2-4C) or alkynyl (2-4C),

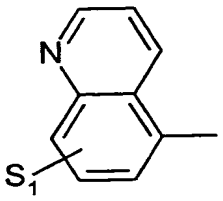
or 3) a group of the formula



(3)

wherein S_1 has the above meaning and Z is C, O or N,

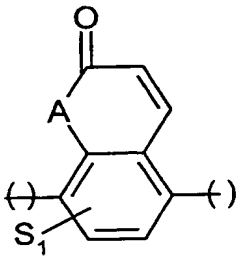
or 4) a group of the formula



(4)

wherein S_1 has the above meaning,

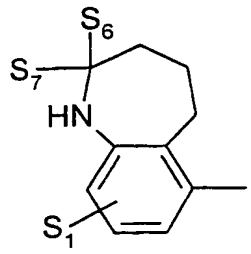
or 5) a group of the formula



(5)

wherein S_1 has the above meaning and A is O or N, linked to the piperazine ring with position 5 or 8,

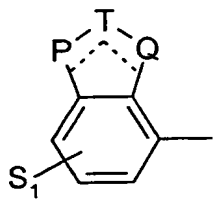
or 6) a group of the formula



(6)

wherein S_1 has the above meaning and S_6 and S_7 represent hydrogen atoms or an oxo group,

or 7) a group of the formula



(7)

wherein one of the dotted lines can represent a double bond, S_1 has the above meaning, and

P=T=Q=nitrogen

or P=T=nitrogen and Q=C

or P=Q=nitrogen and T=C or C-CH_3

or P=nitrogen, and T and Q are carbon

or P=nitrogen, T is carbon and Q is sulphur

- m has the value 2 to 6;
- n has the value 0-2;
- R_5 and R_6 are independently H or alkyl (1-3C); or R_5+R_6 represent a group $-(CH_2)_p-$ wherein p has the value 3-5, and
- R_7 is alkyl (1-3C), alkoxy (1-3C), halogen or cyano; or R_6+R_7 (R_7 at position 7 of the indole group) represent a group $-(CH_2)_q$ wherein q has the value 2-4,

and salts thereof, which show high affinity for the dopamine D_2-receptor and are good serotonin reuptake inhibitors (SRI's).

Preferred compounds of the invention are compounds having formula (I) wherein X represents a group of the formula (1), (2) or (3), wherein the symbols have the meanings given above and the salts thereof.

Especially preferred are compounds having formula (I) wherein X is the group with the formula (1) wherein S_1=H, S_2=CH_3, S_3=H, S_4=oxo, S_5=H and Y is oxygen, m is 3, R_5=R_6=hydrogen, n is 0 or 1 and R_7 is 5-fluoro,
and the salts thereof.

It has been found that the compounds according to the invention show high affinity for both the dopamine D_2 receptor and the serotonin reuptake site. This combination is useful for the treatment of schizophrenia and other psychotic disorders which enables a more complete treatment of all disease symptoms (e.g. positive symptoms and negative symptoms).

However, some of the compounds having formula (I) show (partial) agonist activity at dopamine receptors making them particularly suitable for the treatment of Parkinson's disease.

The compounds show activity as antagonists at dopamine D_2 receptors as they potentially antagonize apomorphine-induced climbing behaviour in mice. The compounds also show activity as inhibitors of serotonin reuptake, as they potentiate 5-HTP induced behaviour in mice.

The compounds are active in therapeutic models sensitive to clinically relevant antipsychotics (e.g. the conditioned avoidance response; Van der Heyden & Bradford, Behav. Brain Res., 1988, 31:61-67) and antidepressants or anxiolytics (e.g. suppression of stress-induced vocalization; van der Poel et al., Psychopharmacology, 1989, 97: 147-148).

In contrast to clinically relevant dopamine D_2 receptor antagonists the described compounds have a low propensity to induce catalepsy in rodents and as such are likely to induce less extrapyramidal side effects than existing antipsychotic agents.

The inhibitory activity of serotonin reuptake inherent in these compounds may be responsible for the therapeutic effects observed in behavioural models sensitive to either antidepressants or anxiolytics.

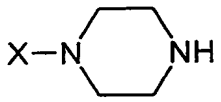
The compounds can be used for the treatment of affections or diseases of the central nervous system caused by disturbances in either the dopaminergic or serotonergic systems, for example: aggression, anxiety disorders, autism, vertigo, depression, disturbances of cognition or memory, Parkinson's disease, and in particular schizophrenia and other psychotic disorders.

Pharmacologically acceptable acids with which the compounds of the invention can form suitable acid addition salts are for example hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, and organic acids such as citric acid, fumaric acid, maleic acid, tartaric acid, acetic acid, benzoic acid, p-toluene sulphonic acid, methanesulphonic acid and naphthalene sulphonic acid.

When the compounds comprise a centre of chirality both the racemic mixture and the individual enantiomers belong to the invention.

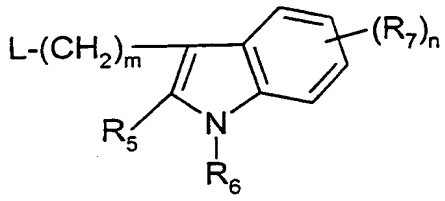
The compounds and their acid addition salts can be brought into forms suitable for administration by means of suitable processes using auxiliary substances such as liquid and solid carrier materials.

The compounds having formula (I) can be prepared by reaction of a compound of the formula



(II)

under basic conditions with a compound of the formula

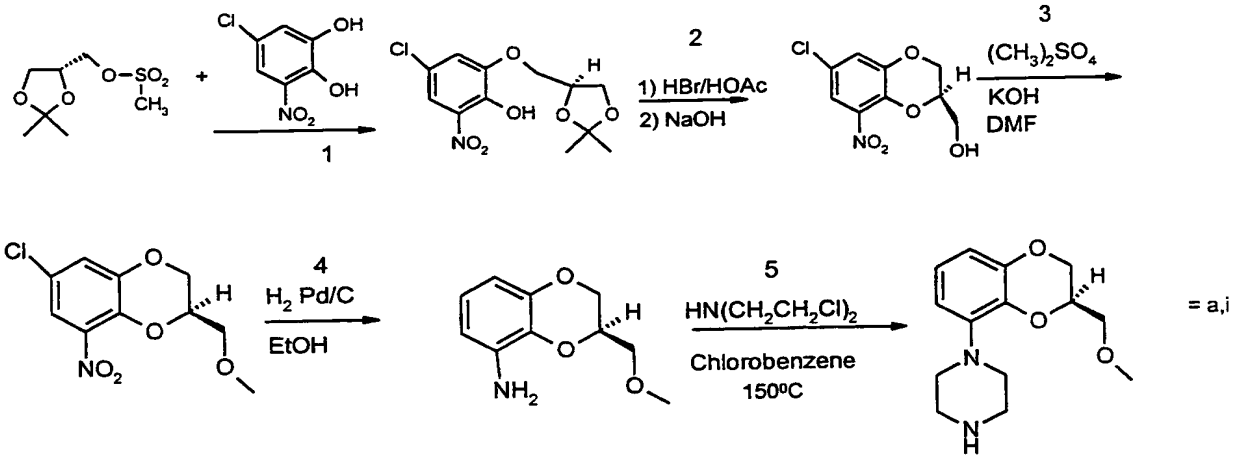


(III)

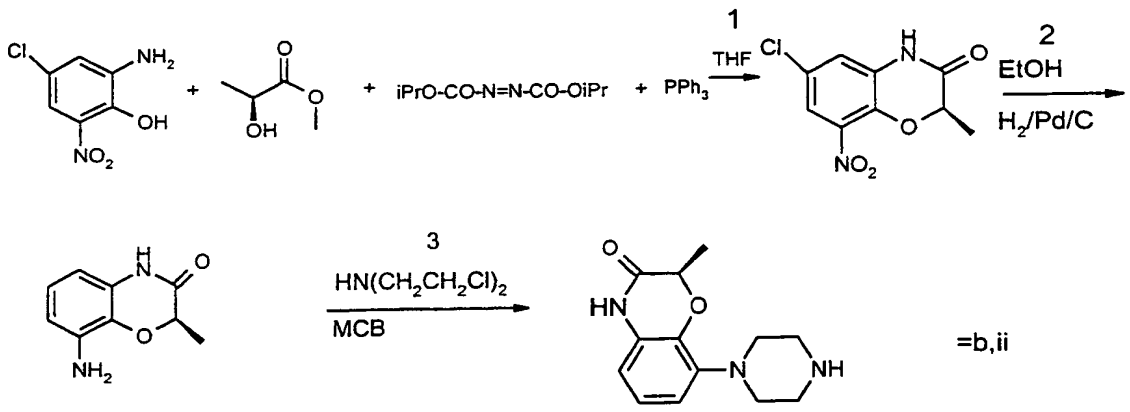
in which formulae the symbols have the meanings given above, and L is a so-called leaving group such as a halogen atom or a mesylate group.

The piperazine compounds having formula (II) can be obtained as described in EP 0138280, EP 0189612 and/or EP 0900792, or in an analogous manner.

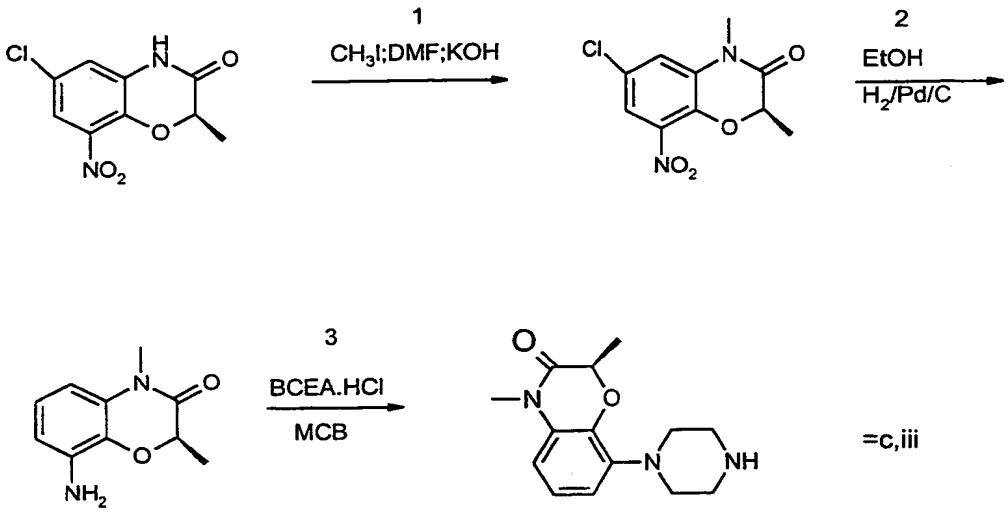
The preparation of the piperazines having formula (II) can be carried out as indicated in schemes (i)-(iv) below. Some of the routes result in optically pure piperazine derivatives.



Scheme (i)

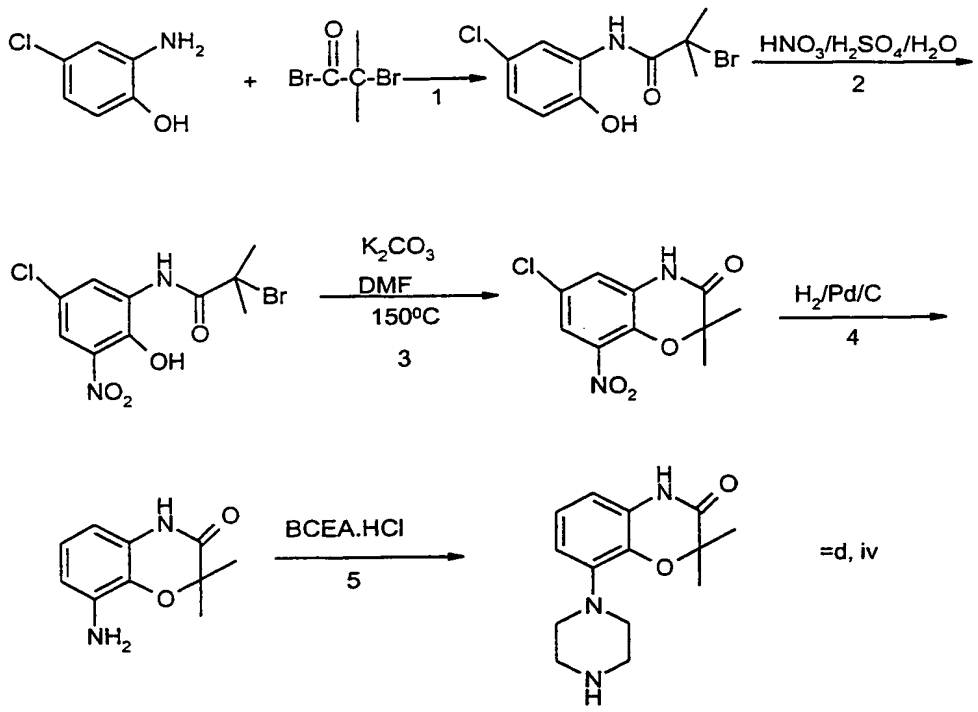


Scheme (ii)



Scheme (iii)

5



Scheme (iv)

The starting compounds having formula (III) can be prepared according to methods known for analogues compounds, as described for example in Organic Process Res. and Dev. 1997 (1), 300-310.

The invention will now be illustrated by means of the following Examples:

Example 1: preparation of compound a,i (see scheme i)

Step 1 (scheme i): To a solution of chloronitrocatechol (6.45 g , 34 mmol) in dry DMSO (50 ml) was added powdered NaOH (2.72 g , 68 mmol). After stirring for 30 minutes a solution was added of R-glycerolketal mesylate (8.0 g, 38 mmol) in DMSO (20 ml) and this mixture was heated at 80°C during 24 hours. After cooling to room temperature the reaction mixture was poured into water (200 ml), acidified with 1N HCl and extracted with methyl t-butylether. The organic fraction was washed with water and dried on $MgSO_4$. After removal of the drying agent and the solvent *in vacuo*, the resulting oil was subjected to flash chromatografy (SiO_2, eluent PE/aceton=3/1). Yield 9.29 g (90%) of the S-ketal.

Step 2 (scheme i): To a solution of the S-ketal (31 g, 102 mmol) in acetic acid (120 ml) was added 35% HBr in acetic acid (80 ml) and this mixture was rotated for 2 hours on a rotavapor in a waterbath of 50°C. The reaction mixture was diluted with ethanol (96%, 250 ml), cooled in a salt/ice mixture and then NaOH (50% in water, 250 ml) was added slowly, keeping the temperature below 15°C. After adding ethanol (250 ml) and water (250 ml) the reaction mixture was stirred at room temperature for 16 hours. Then concentrated HCl (about 300 ml) and water were added and the mixture extracted with ethyl acetate. After washing the organic fraction with 5% $NaHCO_3$ (4x500 ml), the solvent was removed *in vacuo* and the resulting oil was subjected to flash chromatografy (SiO_2, eluent PE/aceton=3/1).
Yield 20.5 g (81%) of the R-benzodioxane as a yellow oil.

Step 3 (scheme i): To a solution of R-benzodioxane (20 g, 81 mmol) in DMF (200 ml) was added KOH (4.56 g, 81 mmol). After cooling the red solution in ice/aceton dimethyl sulfate (23 ml) was added and the reaction mixture was stirred for 1.5 hours at room temperature. Then more KOH (4.56 g, cooling) was added and the mixture was stirred at room temperature for 16 hours. After adding water (700 ml), the product was extracted with ethyl acetate. The ethyl acetate was removed *in vacuo* and the resulting oil was subjected to flash chromatografy (SiO_2, eluent PE/aceton=4/1) yielding R-methoxymethylbenzodioxane (12.3 g, 58%) as a yellow oil. $[\alpha]_D^{25}$= -97° (methanol).

Step 4 (scheme i): To a solution of R- methoxymethylbenzodioxane (5 g, 19 mmol) in ethanol (100 ml) and ethyl acetate (50 ml) was added a catalytic amount of 10% Pd/C and the solution was shaken under atmospheric H_2 pressure at room temperature. After the calculated amount of H_2 was taken up by the reaction mixture, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. Yield 3.7 g (100%) of the corresponding anilino-compound.

Step 5 (scheme i): The anilino-compound (4 g, 2 mmol) and BCEA, i.e. $HN(CH_2CH_2Cl)_2.HCl$ (3.7 g , 2 mmol) were dissolved in chlorobenzene (100 ml). The mixture was heated to 150°C for 16 hours, concentrated *in vacuo* and purified by flash chromatografy (SiO_2 , dichloromethane/methanol/ammonium hydroxide=92/7.5/0.5).
Yield 3.67 g (68%) of the piperazine a.i.

Example 2: preparation of compound no. 126

The route is described above, i.e. reaction of compound (II) with compound (III). The mesylates of formula (III) were prepared from the corresponding alcohols by standard procedures, *e.g.* with $MsCl/Et_3N$.

A mixture of the piperazine a,i (3,6 g , 13,6 mmol) , the 5-fluoro indole-mesylate (4,1 g , 15,1 mmol), triethylamine (2 ml) and a catalytic amount of KI in CH_3CN (100 ml) was heated under reflux during 18 hours after which the reaction mixture was concentrated *in vacuo* and purified by chromatografy (SiO_2 , dichloromethane/methanol/ammonium hydroxide =92/7.5/0.5). Yield 3,77 of the free base (oil). The free base was dissolved in ethanol and 1 equivalent of fumaric acid in ethanol was added. After removal of the solvent compound no. 126 was obtained (4,3 g, 57%). $[\alpha]_D^{25} = -2°$ (methanol)

Example 3 : preparation of compound b,ii (see scheme ii)

Step 1 (scheme ii): A solution of the aminophenol (37.3 g, 198 mmol), S-lactic acid methyl ester (20 ml) and triphenylphosphine (58 g, 220 mmol) in THF (2000 ml) was cooled in ice/salt (temperature <10°C). Then a solution of azodicarboxic acid ester (DIAD, 43 ml , 218 mmol) in THF (400 ml) was added slowly. After stirring at room temperature for 18 hours the reaction mixture was concentrated *in vacuo* and ethanol (500 ml) and 36% HCl (125 ml) were added to the residue. The mixture was heated to 100°C (development of gas). After cooling the compound was isolated by filtration and washed with 96% ethanol (about 100 ml). Yield 42 g (87%).

Step 2 (scheme ii): This step is similar to step 4 described in scheme i.

Step 3 (scheme ii): This step is similar to step 5 described in scheme i, resulting in the formation of the piperazine b,ii.

Example 4: preparation of compound no. 89

The route is described above, i.e. reaction of compound (II) with compound (III). The reaction is carried out as described in example 2, starting with the piperazine b,ii . Yield 58% of compound no. 89, $[\alpha]_D^{25} = -24°$ (methanol).

Example 5: preparation of coumpound c,iii (see scheme iii)

Step 1 (scheme iii): A solution of the benzomorpholinone (10 g , 41 mmol ; see scheme ii, step 1) and powdered KOH (2.3 g , 41 mmol) in DMF (100 ml) was cooled in ice (temperature <10°C). After adding 1 equivalent of MeI (2.55 ml, 41 mmol) the reaction mixture was stirred at room temperature for about 1.5 hours and then poured into water. The precipitate was filtered off, washed with water and dried. Yield 10 g (95%) of the NCH_3-compound, mp. 191-192; $[\alpha]_D^{25}$ = +7.5° (in THF)

Step 2 (scheme iii): This step is similar to step 4 described in scheme i.

Step 3 (scheme iii): This step is similar to step 5 described in scheme i, resulting in the formation of the piperazine c,iii.

Example 6 : preparation of compound no. 121

The route is described above, i.e. reaction of compound (II) with compound (III). The reaction is performed as described in example 2, starting with the piperazine c,iii . Yield 44% of compound no. 121, $[\alpha]_D^{25}$ = -28° (methanol).

Example 7: preparation of compound d,iv (see scheme iv)

Step 1 (scheme iv): Pyridine (81ml, 1 mol) was added to a solution of 2-hydroxy-5-chloroaniline (143.5 g, 1 mol) in dry CH_2Cl_2. The mixture was cooled in ice (temperature <10°C) and then a solution of 2-bromo-2-methyl-propionylbromide (163 ml, 1 mol) in CH_2Cl_2 (100 ml) was added slowly. The mixture was stirred at room temperature for 18 hours and was poured into CH_2Cl_2 (5000 ml) and water (2000 ml). The organic layer was washed with water, dried and concentrated *in vacuo* till about 1 litre. The precipitate was filtered off, washed with CH_2Cl_2 and dried. Yield 231 g (79%) of the bromocompound, mp. 172°C.

Step 2 (scheme iv): To a suspension of the bromocompound (60 g , 205 mmol) in water (95 ml) was added slowly under ice cooling concentrated sulfuric acid (7 ml) followed by 70% HNO_3 (16 ml) and stirring was continued for 2 hours at room temperature. After cooling in ice water the precipitate was filtered off, washed with water and purified by chromatografy (SiO_2, methyl t-butylether). Yield 49 g (71%) of the nitrocompound.

Step 3 (scheme iv): To a solution of the nitrocompound (49 g , 145 mmol) in DMF (500ml) was added K_2CO_3. This mixture was heated for one hour at 150°C, then cooled and poured into a mixure water / ethyl acetate.The organic fraction was washed with sodium bicarbonate (5% in water) , HCl (2N) and water respectively. The solvent was removed *in vacuo* and the residue was purified by flash chromatografy (SiO_2 , methyl t-butylether / PE = 1 / 1). Yield 23 g (62%).

Step 4 (scheme iv): This step is similar to step 4 described in scheme i.

Step 5 (scheme iv): This step is similar to step 5 described in scheme i, leading to the formation of the piperazine d,iv.

Example 8: preparation of compound no. 115

The route is described above, i.e. reaction of compound (II) with compound (III). The reaction is performed as described in example 2, starting with the piperazine d,iv . Yield 20% of compound no. 115.

The compounds listed in the following tables have been prepared according to the method of the above examples.

Comp. no	X	m	Y	R_5	R_6	$(R_7)n$	R	Z	A	S_6+S_7	P	T	Q	Remarks
1	form 2	3	-	H	H	H	2-CH_2OH	-	-	-	-	-	-	S_1=H
2	1	3	C	H	H	H	-	-	-	-	-	-	-	S_1-S_5=H
3	3	3	-	H	H	H	-	O	-	-	-	-	-	S_1=H
4	3	4	-	H	H	H	-	O	-	-	-	-	-	S_1=H
5	3	4	-	H	H	H	-	O	-	-	-	-	-	S_1=H
6	3	3	-	H	CH_3	H	-	O	-	-	-	-	-	S_1=H
7	2	3	-	H	H	H	3-CH_2OH	-	-	-	-	-	-	S_1=H
8	1	3	O	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_1=S_2=S_3=S_5=H
9	1	3	O	H	H	H	-	-	-	-	-	-	-	S_1-S_5=H
10	4	3	-	H	H	H	-	-	-	-	-		-	S_1=H
11	1	3	C	H	H	H	-	-	-	-	-	-	-	S_1, S_3-S_5=H S_2=CH_3
12	3	3	-	H	-$(CH_2)_3$-		-	O	-	-	-	-	-	S_1=H
13	2	3	-	H	H	H	3-CH_2OH	-	-	-	-	-	-	S_1=H *
14	1	3	C	-$(CH_2)_4$		H	-	-	-	-	-	-	-	S_1-S_5=H
15	3	3	-	H	H	5-OCH_3	-	O	-	-	-	-	-	S_1=H
16	1	3	C	CH_3	H	5-Cl	-	-	-	-	-	-	-	S_1-S_5=H
17	3	3	-	CH_3	H	5-Cl	-	O	-	-	-	-	-	S_1=H
18	1	3	C	H	H	5-Br	-	-	-	-	-	-	-	S_1-S_5=H
19	3	3	-	H	H	5-Br	-	O	-	-	-	-	-	S_1=H
20	1	2	C	H	H	H	-	-	-	-	-	-	-	S_1-S_5=H
21	1	3	C	H	H	5-F	-	-	-	-	-	-	-	S_1-S_5=H
22	3	3	-	H	H	5-F	-	O	-	-	-	-	-	S_1=H
23	3	3	-	H	H	H	-	CH_2	-	-	-	-	-	S_1=H
24	5	3	-	H	H	H	-	-	O	-	-	-	-	S_1=H; position 8
25	1	3	C	H	H	7-Cl	-	-	-	-	-	-	-	S_1-S_5=H

* R_7 is linked to position 7 of the indole group

5

Comp. no	X	m	Y	R_5	R_6	$(R_7)n$	R	Z	A	S_6+S_7	P	T	Q	Remarks
26	form 3	3	-	H	H	7-F	-	O	-	-	-	-	-	S_1=H
27	1	3	C	H	H	7-F	-	-	-	-	-	-	-	S_1-S_5=H
28	3	3	-	H	H	7-Cl	-	O	-	-	-	-	-	S_1=H
29	3	3	-	H	H	7-CH_3	-	O	-	-	-	-	-	S_1=H
30	2	3	-	H	H	H	2-CH_2OCH_3	-	-	-	-	-	-	S_1=H
31	7	3	-	H	H	H	-	-	-	-	N	CH_2	CH_2	S_1=H
32	1	3	C	H	H	6-Cl	-	-	-	-	-	-	-	S_1-S_5=H
33	3	3	-	H	H	6-Cl	-	O	-	-	-	-	-	S_1=H
34	3	3	-	H	H	5-CN	-	O	-	-	-	-	-	S_1=H
35	1	3	C	H	H	5-CN	-	-	-	-	-	-	-	S_1.S_5=H
36	1	3	C	H	H	4-Cl	-	-	-	-	-	-	-	S_1-S_5=H
37	3	3	-	H	H	4-Cl	-	O	-	-	-	-	-	S_1=H
38	1	6	C	H	H	H	-	-	-	-	-	-	-	S_1-S_5=H
39	1	5	C	H	H	H	-	-	-	-	-	-	-	S_1-S_5=H
40	1	3	C	H	H	H	-	-	-	-	-	-	-	S_1-S_4=H S_5=CH_3
41	1	3	S	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_1-S_3=S_5=H
42	6	3	-	H	H	H	-	-	-	oxo	-	-	-	S_1=H
43	1	3	S	H	H	H	-	-	-	-	-	-	-	S_1-S_5=H
44	6	3	-	H	H	H	-	-	-	H_2	-	-	-	S_1=H
45	1	4	C	H	H	H	-	-	-	-	-	-	-	S_1-S_5=H
46	1	3	C	H	H	6-F	-	-	-	-	-		-	S_1-S_5=H
47	3	3	-	H	H	6-F	-	O	-	-	-	-	-	S_1=H
48	7	3	-	H	H	H	-	-	-	-	N	CH	NH	S_1=H
49	1	3	O	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_2=CH_3, S_1=S_3=S_5=H
50	1	3	C	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_1-S_3=S_5=H

Comp. no	X	m	Y	R_5	R_6	$(R_7)n$	R	Z	A	S_6+S_7	P	T	Q	Remarks
51	form 3	3	-	H	C_2H_5	5-CN	-	O	-	-	-	-	-	S_1=H
52	3	3	-	H	H	H	-	NH	-	-	-	-	-	S_1=H
53	7	3	-	H	H	H	-	-	-	-	N	$C(CH_3)$	NH	S_1=H
54	7	3	-	H	H	H	-	-	-	-	NH	N	CH	S_1=H
55	7	3	-	H	H	H	-	-	-	-	N	N	NH	S_1=H
56	1	3	C	H	H	4-F	-	-	-	-	-	-	-	S_1-S_5=H
57	3	3	-	H	H	4-F	-	O	-	-	-	-	-	S_1=H
58	1	3	C	H	H	7-Br	-	-	-	-	-	-	-	S_1-S_5=H
59	3	3	-	H	H	7-Br	-	O	-	-	-	-	-	S_1=H
60	1	3	O	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_1=7-Cl, S_2=S_3=S_5=H
61	2	3	-	H	H	5-F	$2\text{-}CH_2OCH_3$	-	-	-	-	-	-	S_1=H
62	1	3	C	H	H	$5,7\text{-}F_2$	-	-	-	-	-	-	-	S_1-S_5=H
63	3	3	-	H	H	$5,7\text{-}F_2$	-	O	-	-	-	-	-	S_1=H
64	2	3	-	H	H	7-F	$2\text{-}CH_2OCH_3$	-	-	-	-	-	-	S_1=H
65	5	3	-	H	H	H	-	-	NH	-	-	-	-	S_1=H; position 5
66	5	3	-	H	H	5-F	-	-	NH	-	-	-	-	S_1=H; position 5
67	5	3	-	H	H	7-F	-	-	NH	-	-	-	-	S_1=H; position 5
68	2	3	-	H	H	H	$3\text{-}CH_2OCH_3$	-	-	-	-	-	-	S_1=H
69	2	3	-	H	H	H	$2\text{-}CH_2OCH_3$	-	-	-	-	-	-	S_1=H
70	2	3	-	H	H	5-F	$2\text{-}CH_2OCH_3$	-	-	-	-	-	-	S_1=H
71	2	3	-	H	H	5-F	$3\text{-}CH_2OCH_3$	-	-	-	-	-	-	S_1=H
72	2	3	-	H	H	7-F	$3\text{-}CH_2OCH_3$	-	-	-	-	-	-	S_1=H
73	2	3	-	H	H	7-F	$2\text{-}CH_2OCH_3$	-	-	-	-	-	-	S_1=H
74	1	3	S	H	H	5-F	-	-	-	-	-	-	-	S_4=oxo, S_1-S_3=S_5=H
75	2	3	-	H	H	H	$3\text{-}CH_2OC_3H_7$	-	-	-	-	-	-	S_1=H

Comp. no	X	m	Y	R_5	R_6	$(R_7)n$	R	Z	A	S_6+S_7	P	T	Q	Remarks
76	form.2	3	-	H	H	5-F	3-$CH_2OC_3H_7$	-	-	-	-	-	-	S_1=H
77	2	3	-	H	H	H	3-$CH_2OCH_2C{\equiv}CH$	-	-	-	-	-	-	S_1=H
78	2	3	-	H	H	5-F	3-$CH_2OCH_2C{\equiv}CH$	-	-	-	-	-	-	S_1=H
79	2	3	-	H	H	7-F	3-$CH_2OCH_2C{\equiv}CH$	-	-	-	-	-	-	S_1=H
80	2	3	-	H	H	H	3-$CH_2OCH_2CH_2OCH_3$	-	-	-	-	-	-	S_1=H
81	2	3	-	H	H	5-F	3-$CH_2OCH_2CH_2OCH_3$	-	-	-	-	-	-	S_1=H
82	2	3	-	H	H	7-F	3-$CH_2OCH_2CH_2OCH_3$	-	-	-	-	-	-	S_1=H
83	1	3	S	H	H	5-F	-	-	-	-	-	-	-	S_1-S_5=H
84	1	3	S	H	H	H	-	-	-	-	-	-	-	S_2=CH_3,S_1=S_3-S_5=H
85	1	3	S	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_2=CH_3, S_1=S_3=S_5=H
86	7	3	-	H	H	H	-	-	-	-	N	CH	S	S_1=H
87	1	3	O	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_2=CH_3, S_1=S_3=S_5=H
88	1	3	O	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_2=CH_3, S_1=S_3=S_5=H
89	1	3	O	H	H	5-F	-	-	-	-	-	-	-	S_4=oxo, S_2=CH_3, S_1=S_3=S_5=H
90	1	3	O	H	H	5-F	-	-	-	-	-	-	-	S_4=oxo, S_2=CH_3, S_1=S_3=S_5=H
91	1	3	O	H	H	7-F	-	-	-	-	-	-	-	S_4=oxo, S_2=CH_3, S_1=S_3=S_5=H
92	1	3	O	H	H	7-F	-	-	-	-	-	-	-	S_4=oxo, S_2=CH_3, S_1=S_3=S_5=H
93	1	3	O	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_2= phenyl, S_1=S_3=S_5=H
94	1	3	O	H	H	5-F	-	-	-	-	-	-	-	S_4=oxo, S_2= phenyl, S_1=S_3=S_5=H
95	1	3	O	H	H	7-F	-	-	-	-	-	-	-	S_4=oxo, S_2= phenyl, S_1=S_3=S_5=H
96	2	3	-	H	H	H	3-$CH_2OCH_2CH{=}CH_2$	-	-	-	-	-	-	S_1=H
97	2	3	-	H	H	5-F	3-$CH_2OCH_2CH{=}CH_2$	-	-	-	-	-	-	S_1=H
98	2	3	-	H	H	7-F	3-$CH_2OCH_2CH{=}CH_2$	-	-	-	-	-	-	S_1=H
99	2	3	-	H	H	H	2-$CH_2OCH_2C{\equiv}CH$	-	-	-	-	-	-	S_1=H
100	2	3	-	H	H	5-F	2-$CH_2OCH_2C{\equiv}CH$	-	-	-	-	-	-	S_1=H

Comp. no	X	m	Y	R_5	R_6	$(R_7)n$	R	Z	A	S_6+S_7	P	T	Q	Remarks
101	form. 2	3	-	H	H	7-F	2-$CH_2OCH_2C\equiv CH$	-	-	-	-	-	-	S_1=H
102	1	3	O	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_2=C_3H_7, S_1=S_3=S_5=H
103	1	3	O	H	H	5-F	-	-	-	-	-	-	-	S_4=oxo, S_2=C_3H_7, S_1=S_3=S_5=H
104	1	3	O	H	H	7-F	-	-	-	-	-	-	-	S_4=oxo, S_2=C_3H_7, S_1=S_3=S_5=H
105	1	3	O	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_2=S_5=CH_3, S_1=S_3=H
106	1	3	O	H	H	5-F	-	-	-	-	-	-	-	S_4=oxo, S_2=S_5=CH_3, S_1=S_3=H
107	1	3	O	H	H	7-F	-	-	-	-	-	-	-	S_4=oxo, S_2=S_5=CH_3, S_1=S_3=H
108	1	3	O	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_2=benzyl, S_1=S_3=S_5=H
109	1	3	O	H	H	5-F	-	-	-	-	-	-	-	S_4=oxo, S_2=benzyl, S_1=S_3=S_5=H
110	1	3	O	H	H	7-F	-	-	-	-	-	-	-	S_4=oxo, S_2=benzyl, S_1=S_3=S_5=H
111	2	3	-	H	H	H	3-$CH_2OCH_2C\equiv CCH_3$	-	-	-	-	-	-	S_1=H
112	2	3	-	H	H	H	2-$CH_2OCH_2C\equiv CCH_3$	-	-	-	-	-	-	S_1=H
113	2	3	-	H	H	5-F	2-$CH_2OCH_2C\equiv CCH_3$	-	-	-	-	-	-	S_1=H
114	1	3	O	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_2=S_3=CH_3, S_1=S_5=H
115	1	3	O	H	H	5-F	-	-	-	-	-	-	-	S_4=oxo, S_2=S_3=CH_3, S_1=S_5=H
116	2	3	-	H	H	H	3-CH_2OCH_3	-	-	-	-	-	-	S_1=H
117	2	3	-	H	H	5-F	3-CH_2OCH_3	-	-	-	-	-	-	S_1=H
118	2	3	-	H	H	5-F	3-CH_2OCH_3	-	-	-	-	-	-	S_1=H
119	2	3	-	H	H	H	3-CH_2OCH_3	-	-	-	-	-	-	S_1=H
120	1	3	O	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_2=S_5=CH_3,S_1=S_3=H
121	1	3	O	H	H	5-F	-	-	-	-	-	-	-	S_4=oxo, S_2=S_5=CH_3,S_1=S_3=H
122	1	3	O	H	H	5-F	-	-	-	-	-	-	-	S_4=oxo, S_2=S_5=CH_3,S_1=S_3=H
123	1	3	O	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_2=S_5=CH_3,S_1=S_3=H
124	1	3	O	H	H	5-F	-	-	-	-	-	-	-	S_4=oxo, S_1=7-Cl, S_2=S_3=S_5=CH_3
125	1	3	O	H	H	5-F	-	-	-	-	-	-	-	S_4=oxo, S_1=H,S_2=S_3=S_5=CH_3
126	2	3	-	H	H	5-F	3-CH_2OCH_3	-	-	-	-	-	-	S_1=H

Comp. no	Salt or free base	MP(°C)	$[\alpha]_D^{25}$ (in methanol)
1	fumarate	192-4	-
2	2-HCl	239-41	-
3	free base	203-4	-
4	"	170-1	-
5	3.fumarate	98	-
6	free base	175-6	-
7	4/3. fumarate	140-3	-
8	free base	189-90	-
9	fumarate	200-1	-
10	3/2. fumarate	190-1	-
11	½ .fumarate	210-2 (dec.)	-
12	free base	165-7	-
13	free base	70-1	-
14	fumarate	208	-
15	free base	amorph	-
16	2. fumarate	amorph	-
17	free base	amorph	-
18	fumarate	>225 (dec.)	-
19	fumarate	>170 (dec.)	-
20	free base	amorph	-
21	½. fumarate	>245 (dec)	-
22	½. fumarate	>165 glass)	-
23	free base	176-7	-
24	free base	amorph	-
25	½. fumarate	amorph	-
26	¾. fumarate	amorph	-
27	½. fumarate	> 240 (dec)	-
28	4/5. fumarate	amorph	-
29	"	amorph	-
30	3/2. fumarate	glass	-
31	5/4. fumarate	188-190	-
32	½. fumarate	>230 (dec)	-
33	fumarate	amorph	-
34	fumarate	150-2	-
35	½. fumarate	247-8 (dec)	-
36	½. fumarate	>240 (dec)	-
37	fumarate	amorph	-
38	HCl	amorph	-
39	HCl	amorph	-
40	HCl	220-4	-
41	HCl	>250 (dec)	-
42	½. fumarate	214-7(dec)	-
43	½. fumarate	240-3	-
44	½. fumarate	220-2(dec)	-
45	HCl	amorph	-
46	fumarate	223-5	-
47	2/3. fumarate	200-2	-
48	free base	glass	-
49	free base	196-7	-
50	free base	181-2	-

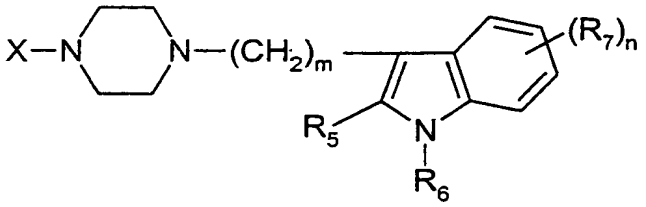
Comp. no	Salt or free base	MP(°C)	$[\alpha]_D^{25}$ (in methanol)
51	½. fumarate	138.5-41	-
52	free base	190-5(dec)	-
53	free base	glass	-
54	free base	glass	-
55	free base	glass	-
56	½. fumarate	185-6	-
57	fumarate	210-1(dec)	-
58	2. fumarate	amorph	-
59	free base	amorph	-
60	½. fumarate	>250	-
61	fumarate	glass	-
62	½. fumarate	245-7	-
63	3/2.fumarate	175-8	-
64	fumarate	glass	-
65	free base	220-4(dec)	-
66	free base	234-6(dec)	-
67	free base	>280	-
68	HCl	glass	-
69	fumarate	glass	+28 (free base), R-conf.
70	fumarate	glass	+28 (free base), R-conf.
71	fumarate	glass	-
72	fumarate	glass	-
73	fumarate	glass	+25 (free base), R-conf.
74	free base	212.5-14.5	-
75	fumarate	glass	-
76	fumarate	glass	-
77	fumarate	glass	-
78	fumarate	glass	-
79	fumarate	glass	-
80	fumarate	glass	-
81	fumarate	glass	-
82	fumarate	glass	-
83	fumarate	amorph	-
84	free base	amorph	-
85	free base	amorph	-
86	½. fumarate	218-20	-
87	free base	glass	-26 R-conf.
88	free base	glass	+27 S-conf.
89	free base	glass	-24 R-conf.
90	free base	glass	+24 S-conf.
91	free base	184-5	-25 R-conf.
92	free base	181-3	+25 S-conf.
93	free base	glass	-
94	free base	glass	-
95	free base	glass	-
96	free base	70-3	-
97	free base	73-5	-
98	fumarate	glass	-
99	fumarate	glass	+39 (free base), R-conf.
100	fumarate	glass	+36 (free base), R-conf.

Comp. no	Salt or free base	MP(°C)	$[\alpha]_D^{25}$ (in methanol)
101	fumarate	glass	+37 (free base), R-conf.
102	free base	158-60	-
103	free base	181-2	-
104	free base	174-6	-
105	free base	glass	-
106	free base	glass	-
107	free base	glass	-
108	free base	glass	-
109	free base	207-10(dec)	-
110	free base	197-9(dec)	-
111	fumarate	glass	-
112	fumarate	glass	+31 (free base), R-conf
113	fumarate	glass	+31 (free base), R-conf
114	free base	191-4	-
115	free base	190-2	-
116	free base	amorph	0 S-conf.
117	fumarate	amorph	S-conf.
118	free base	amorph	R-conf.
119	free base	amorph	0 R-conf.
120	free base	amorph	-31 R-conf.
121	free base	amorph	-28 R-conf.
122	free base	amorph	+28 S-conf.
123	free base	amorph	+32 S-conf.
124	free base	amorph	-
125	free base	amorph	-
126	fumarate	amorph	-2 R-conf.

Claims

1. The invention relates to a group of novel phenylpiperazine derivatives of the formula

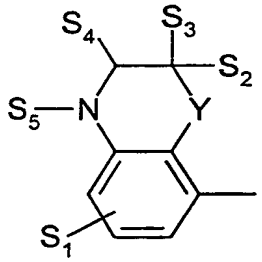
(I):



(I)

wherein:

- X is 1) a group of the formula

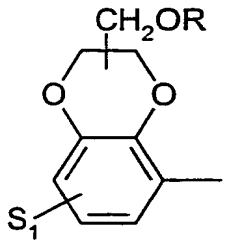


(1)

wherein

- S_1 is hydrogen or halogen,
- S_2 and S_3 are independently hydrogen, alkyl (1-6C), phenyl or benzyl,
- S_4 represents two hydrogen atoms or an oxo group,
- S_5 is H or alkyl (1-4C), and
- Y is C, O or S,

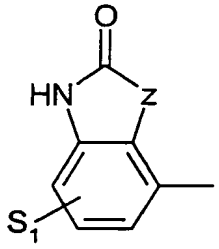
or 2) a group of the formula



(2)

wherein S_1 has the above meaning and R is H, alkyl (1-4C), alkoxyalkyl (2-6C), alkenyl (2-4C) or alkynyl (2-4C),

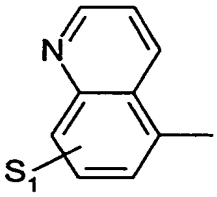
or 3) a group of the formula



(3)

wherein S_1 has the above meaning and Z is C, O or N,

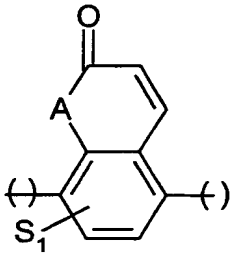
or 4) a group of the formula



(4)

wherein S_1 has the above meaning,

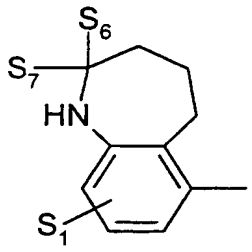
or 5) a group of the formula



(5)

wherein S_1 has the above meaning and A is O or N, linked to the piperazine ring with position 5 or 8,

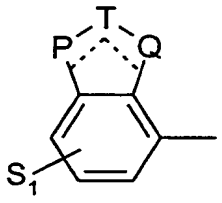
or 6) a group of the formula



(6)

wherein S_1 has the above meaning and S_6 and S_7 represent hydrogen atoms or an oxo group,

or 7) a group of the formula



(7)

wherein one of the dotted lines can represent a double bond, S_1 has the above meaning, and

P=T=Q=nitrogen

or P=T=nitrogen and Q=C

or P=Q=nitrogen and T=C or C-CH_3

or P=nitrogen, and T and Q are carbon

or P=nitrogen, T is carbon and Q is sulphur

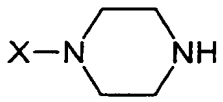
- m has the value 2 to 6;
- n has the value 0-2;
- R_5 and R_6 are independently H or alkyl (1-3C); or R_5+R_6 represent a group $-(CH_2)-_p$ wherein p has the value 3-5, and
- R_7 is alkyl (1-3C), alkoxy (1-3C), halogen or cyano; or R_6+R_7 (R_7 at position 7 of the indole group) represent a group $-(CH_2)_q$ wherein q has the value 2-4,

and salts thereof.

2. A compound as claimed in claim 1, wherein X represents a group of the formula (1), (2) or (3), wherein the symbols have the meanings given in claim 1.

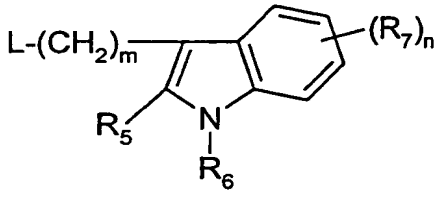
3. A compound as claimed in claim 1, wherein X is the group having formula (I), wherein S_1=S_3=S_5=H, S_4=oxo and S_2=CH_3, m is 3, R_5=R_6=H, n is 0 or 1, and R_7 is 5-fluoro, and salts thereof.

4. Method for the preparation of compounds as claimed in claim 1, characterised in that a compound having formula (II)



(II)

is reacted under basic conditions with a compound having formula (III)



(III)

in which formulae the symbols having the meanings given in claim 1, and L is a so-called leaving group.

5. A pharmaceutical composition containing at least one compound as claimed in claim 1 as an active component.

6. A method of preparing a composition as claimed in claim 5, characterised in that a compound of claim 1 is brought into a form suitable for administration.

7. A method of treating CNS disorders, characterised in that a compound as claimed in claim 1 is used.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 March 2001 (01.03.2001)

PCT

(10) International Publication Number
WO 01/14330 A3

(51) International Patent Classification[7]: C07D 405/12, 401/12, 413/12, 417/12, 209/34, 403/12, 209/40, A61K 31/496

(21) International Application Number: PCT/EP00/08190

(22) International Filing Date: 22 August 2000 (22.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
99202710.2 23 August 1999 (23.08.1999) EP
1012888 23 August 1999 (23.08.1999) NL

(71) Applicant *(for all designated States except US)*: **SOLVAY PHARMACEUTICALS B.V.** [NL/NL]; C.J. Van Houtenlaan 36, NL-1381 CP Weesp (NL).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **VAN HES, Roelof** [NL/NL]; P.O. Box 140, NL-1380 AC Weesp (NL). **VAN DER HEIJDEN, Johannes, A., M.** [NL/NL]; P.O. Box 140, NL-1380 AC Weesp (NL). **KRUSE, Cornelis, G.** [NL/NL]; P.O. Box 140, NL-1380 AC Weesp (NL). **TIPKER, Jacobus** [NL/NL]; P.O. Box 140, NL-1380 AC Weesp (NL). **TULP, Martinus, T., M.** [NL/NL]; P.O. Box 140, NL-1380 AC Weeso (NL). **VISSER, Gerben, M.** [NL/NL]; P.O. Box 140, NL-1380 AC Weesp (NL). **VAN VLIET, Bernard, J.** [NL/NL]; P.O. Box 140, NL-1380 AC Weesp (NL).

(74) Agent: **MUIS, Maarten**; Octrooibureau Zoan B.V., P.O. Box 140, NL-1380 AC Weesp (NL).

(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

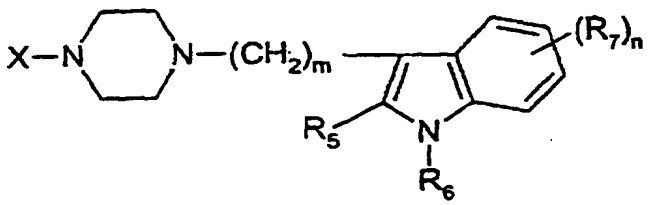
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

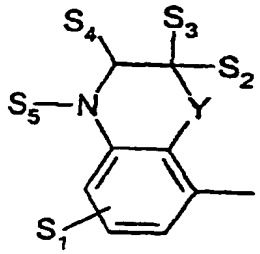
(88) Date of publication of the international search report:
2 August 2001

[Continued on next page]

(54) Title: PHENYLPIPERAZINES AS SEROTONIN REUPTAKE INHIBITORS



(I)



(1)

(57) Abstract: The invention relates to a group of phenylpiperazines having high affinity for the dopamine D2-receptor and are good serotonin reuptake inhibitors (SRI's). The invention relates to a group of phenylpiperazine derivatives of formula (I) wherein: a.o. x is 1) a group of formula (1) wherein: S_1 is hydrogen or halogen; S_2 and S_3 are independently hydrogen, alkyl (1-6C), phenyl or benzyl; S_4 represents two hydrogen atoms or an oxo group, S_5 is H or alkyl (1-4C); and Y is C, O or S, and salts there of.

WO 01/14330 A3

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/08190

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D405/12 C07D401/12 C07D413/12 C07D417/12 C07D209/34
C07D403/12 C07D209/40 A61K31/496

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 99 67237 A (KROG JENSEN CHRISTIAN ;MIKKELSEN IVAN (DK); LUNDBECK & CO AS H (DK) 29 December 1999 (1999-12-29) claims 1,12,14-18; examples 1-5 ---	1,5-7
X	WO 99 05140 A (MIKKELSEN IVAN ;LUNDBECK & CO AS H (DK); MOLTZEN EJNER KNUD (DK);) 4 February 1999 (1999-02-04) claims 1,14-19; examples 1-7 ---	1,5-7
X	DE 197 30 989 A (MERCK PATENT GMBH) 21 January 1999 (1999-01-21) page 1; claims; examples 2-5 ---	1,5-7
Y	EP 0 376 607 A (LUNDBECK & CO AS H) 4 July 1990 (1990-07-04) the whole document; claims; examples 2-5 ---	1,5-7

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 January 2001	23/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bosma, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/08190

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate. of the relevant passages	Relevant to claim No.
Y	DE 43 33 254 A (MERCK PATENT GMBH) 6 April 1995 (1995-04-06) the whole document; claims; examples 2-5	1,5-7
A	DE 41 27 849 A (MERCK PATENT GMBH) 25 February 1993 (1993-02-25) the whole document; claims; examples 2-5	1,5-7

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/08190

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9967237 A	29-12-1999	AU 4359299 A	10-01-2000
WO 9905140 A	04-02-1999	AU 8534098 A	16-02-1999
		BR 9810790 A	25-07-2000
		CN 1265107 T	30-08-2000
		EP 1007523 A	14-06-2000
		NO 20000372 A	21-03-2000
		PL 338194 A	09-10-2000
		ZA 9806237 A	31-03-1999
DE 19730989 A	21-01-1999	AU 8730298 A	10-02-1999
		BR 9810607 A	11-07-2000
		CN 1264379 T	23-08-2000
		WO 9903855 A	28-01-1999
		EP 0998474 A	10-05-2000
		NO 20000216 A	17-01-2000
		PL 338075 A	25-09-2000
		SK 352000 A	12-06-2000
		ZA 9806390 A	24-05-1999
EP 0376607 A	04-07-1990	AT 102184 T	15-03-1994
		AU 637991 B	17-06-1993
		AU 4719889 A	05-07-1990
		CA 2006356 A	28-06-1990
		DE 68913487 D	07-04-1994
		DE 68913487 T	04-08-1994
		DK 645689 A	29-06-1990
		ES 2062050 T	16-12-1994
		FI 93005 B	31-10-1994
		IE 62668 B	22-02-1995
		IL 92990 A	24-01-1995
		JP 2225460 A	07-09-1990
		JP 2895121 B	24-05-1999
		NO 174772 B	28-03-1994
		NZ 231855 A	25-02-1992
		PT 92728 A,B	29-06-1990
		US 5002948 A	26-03-1991
		ZA 8909960 A	28-11-1990
DE 4333254 A	06-04-1995	AT 153663 T	15-06-1997
		AU 679774 B	10-07-1997
		AU 7424494 A	13-04-1995
		BR 1100891 A	06-06-2000
		CA 2133152 A	31-03-1995
		CN 1106811 A,B	16-08-1995
		CZ 9402370 A	12-04-1995
		DE 59402902 D	03-07-1997
		DK 648767 T	22-12-1997
		EP 0648767 A	19-04-1995
		ES 2105454 T	16-10-1997
		GR 3024551 T	31-12-1997
		HU 71833 A	28-02-1996
		JP 7149762 A	13-06-1995
		NO 943616 A	31-03-1995
		PL 305216 A	03-04-1995
		RU 2132848 C	10-07-1999
		SK 118494 A	10-05-1995
		US 5532241 A	02-07-1996

INTERNATIONAL SEARCH REPORT

Information on patent family members

In [redacted]nal Application No
PCT/EP 00/08190

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 4333254 A		ZA 9407622 A	16-05-1995
DE 4127849 A	25-02-1993	AU 653847 B	13-10-1994
		AU 2121092 A	25-02-1993
		CA 2076573 A	23-02-1993
		CZ 9202578 A	17-03-1993
		EP 0529462 A	03-03-1993
		HU 64334 A	28-12-1993
		JP 5230059 A	07-09-1993
		MX 9204844 A	01-04-1993
		NO 923283 A	23-02-1993
		PL 295673 A	17-05-1993
		RU 2056420 C	20-03-1996
		US 5242925 A	07-09-1993
		ZA 9206334 A	22-04-1993